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FOR REVIEW ONLY

TREATMENT OF OVERDISPERSED, AGGREGATED DATA ON HUMAN CHROMOSOMAL ABERRATIONS

MARVIN A. KASTENBAUM: in collaboration with K.O. BOWMAN

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APPLICATION FOR RESEARCH CONTRACT

1. PRINCIPAL INVESTIGATOR. Name, title, telephone # and mailing address.

(a) Marvin A. Kastenbaum (Name) (b) _____ (Title) (c) 813/481-6647 (Telephone number)

(d) _____ (Department) (e) _____ (Institution)

(f) 16933 Timberlakes Drive SW Ft. Myers (Mailing Address) (g) FL33908 (State/Zip)

2. PROJECT TITLE. (Do not exceed 75 typewriter spaces inclusive of spaces between words and punctuation.)

TREATMENT OF OVERDISPERSED, AGGREGATED DATA ON HUMAN CHROMOSOMAL ABERRATIONS

3. KEY WORDS. Please provide three (3) key words which will be used as reference headings.

OVERDISPERSION, AGGREGATED DATA, CHROMOSOMAL ABERRATIONS

4. INSTITUTION. Name and address of institution responsible and accountable for disposition of funds awarded on the basis of this application.

(a) Marvin A. Kastenbaum (Institution) (b) same (Street Address)

(c) _____ (City) (d) _____ (State/Zip)

5. LOCATION. List location where research will be conducted *if other than institution identified in #4 above.*

(a) Oak Ridge National Laboratory - in collaboration with K.O.BOWMAN

(b)

6. INCLUSIVE DATES and TOTAL COSTS of this specific project related to each 12 month period if more than one year is required to complete project. Summarize from budget page, item 13(j). It must be understood that awards for 2nd and 3rd periods are dependent on Science Advisory Board review and Center approval of continuation application.

	Inclusive Date			Total Cost
(a) 1st 12 month period if required	1-1-92	thru	12-31-92	$ 37,500
(b) 2nd 12 month period	1-1-93	thru	12-31-93	$ 38,500
(c) 3rd 12 month period	1-1-94	thru	12-31-94	$ 41,000

7. INSTITUTIONAL OFFICER. Name, title and telephone # of individual authorized to sign for the institution identified in #4 above. It is understood that the officer, in applying for a contract, has read and found acceptable the Center's Management of Research Contracts and Contract Administration Policy.

(a) Marvin A. Kastenbaum (Name) (b) _____ (Title)

(c) 813/481-6647 (Telephone) (d) M. A. Kastenbaum (Signature of institutional officer) (e) April 1, 1991 (Date)

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8. AIMS*. Please be specific. SEE PAGE 7

(a) Hypothesis

(b) Objectives

9. SIGNIFICANCE OF PROPOSED WORK* SEE PAGES 8-9

(a) Background

(b) Literature

(c) Identification of gaps in proposed research area

(d) Project importance

10. PRELIMINARY STUDIES* SEE PAGES 10-14

(a) Feasibility of proposed research

(b) Qualifications of investigator

11. EXPERIMENTAL PLAN* SEE PAGES 10-14

(a) Design

(b) Methods

(c) Analysis of data

(d) Interpretation of results

(e) Timetable for the investigation

(f) Literature cited

12. AVAILABLE FACILITIES AND RESOURCES SEE PAGE 15

12A. OTHER SUPPORT SEE PAGE 15

List all currently active and pending support for all key personnel involved in this proposal. Include the source of support, percentage of appointment, dates of project, a brief description of the project and whether it overlaps, duplicates, replaces, or supplements this proposed work in any way.

* Append as much material as required. TYPE, single space, use 8-1/2" x 11" white paper and label each sheet with name of the principal investigator in upper right hand corner and page number at the bottom. Consecutively number each addendum beginning with page 5. Do not insert pages between pages 1 and 6, e.g. 2a, 2b, 3a, etc. include nine copies and an original. If sending photographs, include 2 original sets.
Note: All nine copies *must* be placed in a press board binder per mailing instructions.

13. BUDGET. Detail specific needs for first 12-month period. Estimate category sub-totals for 2nd and 3rd periods, if required. Append justifications.

(a) Salaries, List personnel by name and title. Indicate individuals % time to be spent on this project.	$ 1st period	$ 2nd period	$ 3rd period
% Professional:			
25 Marvin A. Kastenbaum, Ph.D.		REDACTED	
Technical:			
Other:			
Fringe benefits payable at institution's rate of _____%			
Category (a) Sub-Total		REDACTED	
(b) Consultants (per diem, travel & expenses):			
Prof. L. Roy Shenton, Ph.D. Univ. of Georgia 15 days @ REDACTED		REDACTED	
Category (b) Sub-Total		REDACTED	
(c) Supplies & Expense: Consumables (by category)			
Animals and related costs			
Other expenses (itemize)			
Category (c) Sub-Total	$	$	$
(d) Travel & Expenses:	6,000	6,275	7,000
Category (d) Sub-Total	$ 6,000	$ 6,275	$ 7,000
(e) Alterations and Renovations			
Category (e) Sub-Total	$	$	$
(f) Sub-contracts			
Category (f) Sub-Total	$	$	$

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	Category (g) Sub-Total	$ 1,000	$	$
(g) Equipment	Telephone recorder & FAX	1,000		
(h) TOTAL DIRECT COSTS		$37,500	$38,500	$41,000
(i) Indirect costs not to exceed 25% of the sum of (a) thru (f):		$	$	$
(j) TOTAL PROJECT COSTS	-			

REDACTED

14. BIOGRAPHICAL SKETCH of all professional personnel listed in 13(a). Append. Please include the following: Name, title, education, scientific field, major research interest, research and/or professional experience and publications. (Limit list of publications to the 20 most important and/or relevant.)

APPENDED

15. a) Are HUMAN SUBJECTS to be used in this research? _____ Yes __X__ No

If yes, attach Institutional Review Board approval for procedures involving human subjects.

b) Are LABORATORY ANIMALS to be used in this research? _____ Yes __X__ No

If yes, attach Institutional Animal Care and Use Committee approval for procedures involving animals.

16. If you wish to recommend peer reviewers (outside of your institution) for this proposal, please append their names, addresses, and telephone numbers. Recommendations of peer reviewers are not an application requirement.

Dr. Richard B. Setlow Brookhaven National Laboratory

17. SIGNATURE OF PRINCIPAL INVESTIGATOR: It is understood that the applicant in applying for a Contract has read and found acceptable the Statements of Policy and Terms Under Which Project Contracts Are Made appearing in the application package.

Maria A. Castenholz 4-1-91 Date April 1, 19

Signature of Principal Investigator

rev. 5/90

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OMB No. 0925-0637

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PROTECTION OF HUMAN SUBJECTS ASSURANCE/CERTIFICATION/DECLARATION

☐ ORIGINAL ☐ FOLLOWUP ☐ EXEMPTION (previously undesignated)

☐ GRANT ☐ CONTRACT ☐ FELLOW ☐ OTHER

☐ New ☐ Competing continuation ☐ Noncompeting continuation ☐ Supplemental

APPLICATION IDENTIFICATION NO. *(if known)*

POLICY: A research activity involving human subjects that is not exempt from HHS regulations may not be funded unless an Institutional Review Board (IRB) has reviewed and approved the activity in accordance with Section 474 of the Public Health Service Act as implemented by Title 45, Part 46 of the Code of Federal Regulations (45 CFR 46—as revised). The applicant institution must submit certification of IRB approval to HHS unless the applicant institution has designated a specific exemption under Section 46.101(b) which applies to the proposed research activity. Institutions with an assurance of compliance on file with HHS which covers the proposed activity should submit certification of IRB review and approval with each application. (In exceptional cases, certification may be accepted up to 60 days after the receipt date for which the application is submitted.) In the case of institutions which do not have an assurance of compliance on file with HHS covering the proposed activity, certification of IRB review and approval must be submitted within 30 days of the receipt of a written request from HHS for certification.

1. TITLE OF APPLICATION OR ACTIVITY

2. PRINCIPAL INVESTIGATOR, PROGRAM DIRECTOR, OR FELLOW

3. FOOD AND DRUG ADMINISTRATION REQUIRED INFORMATION *(see reverse side)*

4. HHS ASSURANCE STATUS

☐ This institution has an approved assurance of compliance on file with HHS which covers this activity.

_____ Assurance identification number _____ IRB identification number

☐ No assurance of compliance which applies to this activity has been established with HHS, but the applicant institution will provide written assurance of compliance and certification of IRB review and approval in accordance with 45 CFR 46 upon request.

5. CERTIFICATION OF IRB REVIEW OR DECLARATION OF EXEMPTION

☐ This activity has been reviewed and approved by an IRB in accordance with the requirements of 45 CFR 46, including its relevant Subparts. This certification fulfills, when applicable, requirements for certifying FDA status for each investigational new drug or device. *(See reverse side of this form.)*

_____ Date of IRB review and approval. *(If approval is pending, write "pending." Followup certification is required.)*
(month/day/year)

☐ Full Board Review ☐ Expedited Review

☐ This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by 45 CFR 46 will be reviewed and approved before they are initiated and that appropriate further certification *(Form HHS 596)* will be submitted.

☐ Human subjects are involved, but this activity qualifies for exemption under 46.101(b) in accordance with paragraph _____ *(insert paragraph number of exemption in 46.101(b), 1 through 5)*, but the institution did not designate that exemption on the application.

6. Each official signing below certifies that the information provided on this form is correct and that each institution assumes responsibility for assuring required future reviews, approvals, and submissions of certification.

APPLICANT INSTITUTION	COOPERATING INSTITUTION
NAME, ADDRESS, AND TELEPHONE NO.	NAME, ADDRESS, AND TELEPHONE NO.
NAME AND TITLE OF OFFICIAL *(print or type)*	NAME AND TITLE OF OFFICIAL *(print or type)*
SIGNATURE OF OFFICIAL LISTED ABOVE *(and date)*	SIGNATURE OF OFFICIAL LISTED ABOVE *(and date)*

HHS 596 (Rev. 1/82)

(If additional space is needed, please use reverse side under "Notes.")

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3. FOOD AND DRUG ADMINISTRATION REQUIRED INFORMATION *(from front side)*

According to 45 CFR 46.121, if an application is made to HHS requiring certification and involving use of an investigational new drug or device, additional information is required. In addition, according to 21 CFR 312.1(a)(2), 30 days must elapse between date of receipt by FDA of Form FD-1571 and use of the drug, unless the 30 day delay period is waived by FDA.

3a. INVESTIGATIONAL NEW DRUG EXEMPTION *(if more than one is involved, list others below under NOTES):*

SPONSOR NAME

DRUG NAME

DATE OF END OF 30-DAY EXPIRATION OR WAIVER	NUMBER ISSUED

3b. INVESTIGATIONAL DEVICE EXEMPTION:

SPONSOR NAME

DEVICE NAME

Unless notified otherwise by FDA, under 21 CFR 812.2(b) (ii) a sponsor is deemed to have an approved IDE if: (1) the IRB has agreed with the sponsor that the device is a nonsignificant risk device; and (2) the IRB has approved the study. *(Check applicable box.)*

☐ The IRB agrees with the sponsor that this device is a nonsignificant risk device.

OR

☐ The IDE application was submitted to FDA on *(date)*_____. Number issued_____.

NOTES:

8. AIMS

This document proposes an extension, for a period of three additional years, of the research carried out with CIAR support on the optimal design of laboratory experiments involving mutagenicity tests of chemical components. Our investigations to date have revealed that the problem of overdispersion of binomial and Poisson data, resurrected by us after twenty years of dormancy, is intrinsic to the consideration of experimental-design optimality involving chromosomal aberrations. Moreover, the current literature in genetics reveals that this problem is relevant and important to those geneticists working with large, aggregated data sets. And our own work has shown that this problem is almost certainly susceptible to solution by new and powerful mathematical and statistical techniques.

The tractability of these formerly intractable methods is due, in great part, to computer technology which has evolved in parallel with the collection and aggregation of large quantities of biological data. Techniques of analysis of such data that are currently in vogue - meta-analysis, Poisson-regression, etc. - can no longer rely on the usual simplifying assumptions about underlying distributional properties of the aggregated data. Instead, new distributions that characterize the aggregated data more realistically must be considered and applied. To date, we have developed a number of such distributions (1,2,3), and we are in the process of developing others. We will be applying these distributions to large aggregations of data on human chromosomal aberrations (10,11,12,13). We will also examine the relevancy of our new distributions to recent developments in Poisson-regression. Our findings will be applicable to similar biological endpoints said to result from exposure to environmental tobacco smoke.

9. SIGNIFICANCE OF PROPOSED WORK:

The problem of overdispersion of binomial and Poisson data is intrinsic to the consideration of experimental-design optimality involving human chromosomal aberrations. Recent literature on chromosomal aberrations reveals that this problem is recognized by geneticists who work with large, aggregated data sets(13). They know that statistical analyses to determine the significance of differences in chromosomal aberrations between groups, or experimental treatments, are based on the assumption of an underlying Poisson distribution(16,17) of the data. The validity of such analyses rests on the condition that aberrations in "control cells", (untreated, normal), do indeed follow the Poisson distribution. However, because of the low frequency with which such aberrations arise, this condition has seldom, if ever, been adequately tested. Now, with recently-aggregated, large data sets (11,12,13) such checks on the distributional properties of chromosomal aberrations are practical and feasible.

In human cytogenetics, the collection of large numbers of cells from many individuals involves the participation of many technicians, working in different laboratories, under varying conditions, for long periods of time. All of these factors tend to contribute additional variation, over and above Poisson, to the aggregated numbers upon which statistical tests are ultimately performed. If the aggregated data are assumed to follow a Poisson distribution, the variances are taken to be equal to the means. This fact becomes important in weighted regression analysis and in hypothesis testing. In weighted regression, the weights are generally taken as the inverse of the variance, which, in the case of Poisson variables is equal to the mean. If, by virtue of overdispersion, the weights are too large, the resulting analysis will be distorted.

In the realm of hypothesis testing, the variance, or a function thereof, is featured as the denominator of a ratio, whose numerator is a function of the mean. If additional variation, introduced by the factors mentioned above, is not taken into account, the denominator will be smaller than it should be, and the resulting ratio will be larger. This will

result in a test statistic that rejects the null hypothesis more often than it should. In the parlance of statistics, the Type I error will be increased, and the level of significance will be decreased. For example, if the level of significance is taken as 95%, researchers will conclude that a "significant difference,($p \leq 0.05$)" exists, more often than they should. It also follows that test statistics that are designed to test for adverse effects of environmental hazards (using dose-response analysis) may overstate the significance of effects if overdispersion is present in the data.

These problems and others are alluded to in recent literature (13,14) on observed chromosomal aberrations said to be induced by ionizing radiation. In fact, the same problems would arise when other clastogens are tested for their alleged ability to induce chromosomal aberrations. This concern is especially relevant to chromosomal aberrations, including sister chromatid exchanges in humans (18,19,20,21,22) said to be induced by environmental tobacco smoke.

10-11. PRELIMINARY STUDIES and EXPERIMENTAL PLAN:

To date, we have submitted for publication two manuscripts (1,2), and a third (3) is in its final stages of preparation. Copies of these documents have been forwarded to CIAR as reports of progress of our research accomplishments since January 1990.

Our intent now is to establish close working relationships with other investigators, whose interests in specific aspects of our project will result in collaborations that are of mutual benefit. In particular, Dr. Kastenbaum will establish a collaborative working relationship with Dr. Michael A Bender of the Brookhaven National Laboratory. Dr. Bender possesses and has access to large data sets on human chromosomal aberrations said to be induced by exposure to an assortment of chemical and radiological agents. Analyses have been performed on some subsets of these data, and the results have been reported in the literature (11,12,13). Much work remains to be done, however, specifically in clarifying the various causes of overdispersion associated with some chromosomal aberrations and not with others. Such clarification will make the new and complex distributions, developed by us, more meaningful to the geneticist. Dr. Kastenbaum plans to collaborate with Dr. Bender in this undertaking.

Some of the other questions that will be addressed deal with the nature of the aggregated data, proper approaches to their analysis, and philosophically-acceptable foundations for the inferences drawn from such analyses. Such considerations of these aggregated data will be immediately relevant and applicable to similar data collected in the quest for alleged genetic effects of environmental tobacco smoke.

At the same time, Dr. Bowman will establish a closer working relationship with Dr. E. L. Frome, her colleague at the Oak Ridge National Laboratory. Dr. Frome has published a number of papers on the subject of Poisson-regression (4,5,6,7,8,9), and is an acknowledged expert and leader in this field. The relevance of this collaboration to our proposed project is readily apparent in some of Dr. Frome's publications. His work encompasses the application of Poisson regression techniques to log-linear, quasilinear, and nonlinear models, as well as to epidemiologic follow-up data organized into a life-table type format. Overdispersed Poisson distributions would affect such analyses by virtue of expected changes in the covariance matrix.

One specific application of Frome's work,(6), is a reanalysis of the Doll-Hill data on lung cancer deaths among British physicians. Of particular interest in Frome's analysis is his finding that the treatment of data on nonsmokers is of critical importance to the results of the analysis. Frome demonstrates that estimates of the background death-rate when nonsmoker data are excluded from the analysis, is " seven times lower than the estimate obtained when data for nonsmokers are included." These findings, on the impact of nonsmoker data on the results of epidemiological analyses of the alleged effects of tobacco smoke, are directly relevant to CIAR concerns with the biological effects on nonsmoking humans that are said to result from environmental tobacco smoke.

We will also continue to collaborate with Dr. L.Roy Shenton, (U of GA). His interests in practical analyses of statistical models, especially those dealing with estimation problems associated with distributions, has spanned many years, and, in collaboration with Dr. Bowman, has produced new results using computer-oriented approaches.

REFERENCES

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21. Moore , DH II, Carrano, AV, "Statistical analysis of high SCE frequency in human lymphocytes", Op. cit., 469-480.

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MARVIN A. KASTENBAUM

12-12A. AVAILABLE FACILITIES AND RESOURCES & OTHER SUPPORT:

This research will be carried out in collaboration with K.O. Bowman of the Mathematical Sciences Section-Oak Ridge National Laboratory.

The Oak Ridge National Laboratory is a multi-purpose research institution that includes an Environmental Sciences Division and a Biology Division. The Mathematical Sciences Section of the Engineering and Mathematics Division employs about 35 research personnel with diversified expertise.

MARVIN A. KASTENBAUM

RESEARCH ABSTRACT

Title of Project: TREATMENT OF OVERDISPERSED, AGGREGATED DATA ON HUMAN CHROMOSOMAL ABERRATIONS

Investigators: K.O. Bowman and Marvin A. Kastenbaum

Institution: Oak Ridge National Laboratory (Bowman)

ABSTRACT;

Our investigations to date have revealed that the problem of overdispersion of binomial and Poisson data is intrinsic to the consideration of experimental-design optimality involving chromosomal aberrations alleged to be induced by chemical components in the ambient air. Moreover, the current literature on chromosomal aberrations indicates that the existence of this problem is recognized by geneticists working with large, aggregated data sets. Our research has shown that this problem is almost certainly susceptible to solution by new and powerful mathematical and statistical techniques. Current methods of analysis - meta-analysis, Poisson-regression, etc.- rely on untested, simplifying assumptions about the underlying distributional properties that may not portray the aggregated data accurately. We have developed new, more realistic characterizations (distribution types) that we propose to apply to large aggregations of data on human chromosomal aberrations. Whatever our findings, they will be applicable to similar biological endpoints said to result from exposure to environmental tobacco smoke.

M. A. Kastenbaum 4-1-91
Signature Date

2023524416

CURRICULUM VITAE March 1991

Marvin A. Kastenbaum

MAILING ADDRESS:

REDACTED

EDUCATION

Ph.D.	Statistics, North Carolina State University
M.S.	Statistics, North Carolina State University
B.S.	Mathematics, City College of New York

REDACTED

EMPLOYMENT

1970-1987	Director of Statistics The Tobacco Institute, Washington, D.C.
Summer 1969	Visiting Professor Stanford University, Stanford, California
1968-1970 1960-1967 1956-1960	Special Advisor on Statistics Chief–Biometrics Section Biometrician Oak Ridge National Laboratory, Oak Ridge, Tennessee
1965-1966	Visiting Professor Mathematics Research Center, University of Wisconsin, Madison, Wisconsin
Summer 1955	Consultant Institute of Human Biology, Ann Arbor, Michigan
1953-1954	Biostatistician Atomic Bomb Casualty Commission, Hiroshima, Japan
1952	Chief Statistician Business Information Division, Dun and Bradstreet, Inc., New York, New York
Summers 1948, 1950	Student Assistant Statistician U.S. Bureau of Census, Washington, D.C.

MEMBERSHIP IN PROFESSIONAL SOCIETIES:

- REDACTED
- REDACTED
-

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MEMBERSHIP IN PROFESSIONAL SOCIETIES: (Continued)

- REDACTED
- REDACTED
- REDACTED
-
-
-

OTHER ACADEMIC AND PROFESSIONAL ACTIVITIES:

- Lecturer, North Carolina College, REDACTED
- Traveling Lectures, Oak Ridge National Laboratory, REDACTED
- Lecturer, University of Tennessee, REDACTED
- Professor Biometrical Sciences, University of Tennessee, REDACTED
- Visiting Lecturer, National Science Foundation, REDACTED
- Radiological Animal Research Advisory Committee, U.S. Public Health Service REDACTED REDACTED
- Bureau of Drugs Advisory Committee, Food & Drug Administration, REDACTED
- Advisory Committee on Hazards of Uranium Mining, National Academy of Sciences, Division of Medical Sciences, REDACTED
- Consultant, Climatic Impact Committee, National Academy of Sciences, REDACTED
- Ad hoc Panel on Research Needs for Estimating the Biological Hazards of Low Doses of Ionizing Radiation, National Academy of Sciences, REDACTED
- *Communications in Statistics*, Editorial Board, REDACTED
- Award of Citation Classic Q "Tables for determining the statistical significance of mutation frequencies," *Current Contents*, 20.

PUBLICATIONS (20 selected)

Marvin A. Kastenbaum

With W. C. Moloney (1955), "Leukemogenic effects of ionizing radiation on atomic bomb survivors in Hiroshima City," *Science* 121(3139).

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With K. O. Bowman (1970), "Tables for determining the statistical significance of mutation frequencies," *Mutation Research* 9.

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